Benchmark Goals

The Trans-NIH Action Plan for Liver Disease Research concluded with the description of ten "benchmark" goals. These were cited as goals that were cross-cutting, representative and important. Ultimately, these benchmark goals could be used as a measure of the success of the Action Plan. All ten goals are long-term and not likely to be fully achieved within the first few years after release of the Action Plan. The ten benchmark goals are listed below with a brief statement about progress and prospects for their achievement.

1. Improve success rate of therapy of hepatitis C. The current optimal regimen of therapy for hepatitis C (24-48 weeks on peginterferon plus ribavirin) yields a sustained virological response (long-term eradication of the virus) in 75 to 80 percent of persons with hepatitis C virus (HCV) genotypes 2 and 3 but in only 45 to 50 percent of persons with HCV genotype 1, the most common genotype in the United States. Response rates are lower for other cohorts, including the elderly, African Americans, and persons with HIV infection, renal disease or other co-morbidities. These rates have not improved in the last year. However, several promising HCV-specific protease and polymerase inhibitors have been described recently that are likely to result in improved response rates in the future. Thus, there is general optimism that response rates in hepatitis C will advance appreciably in the next few years as new agents become available that can be given alone or in combination with peginterferon.

2. Develop effective therapies for fatty liver disease, both alcoholic and non-alcoholic. Several large-scale clinical trials of therapy of nonalcoholic steatohepatitis are being designed or are underway that will evaluate the role of weight loss (through such means as behavioral therapy, bariatric surgery, anti-obesity medications), insulin sensitizing agents (e.g., metformin, thiazolidinediones), antioxidants (e.g., vitamin E, betaine), and hepatoprotective agents (silymarin, S-adenosylmethionine). Several of these approaches may also be applicable to alcoholic liver disease. Clearly, new therapies for nonalcoholic steatohepatitis will be developed in the next few years; their degree of efficacy and general applicability remain to be defined.

3. Develop regimens of antiviral therapy that are effective in long-term management of hepatitis B. A total of five medications have been approved for use in chronic hepatitis B in the United States, two within the last year. Licensed therapies include standard interferon alfa, peginterferon, lamivudine, adefovir dipivoxil and entecavir. Preliminary findings using several of the oral nucleoside analogues demonstrate that they can be given long-term and provide sustained benefit. These results require further long-term follow-up and verification. The relative benefits and risks of monotherapy versus combination therapy also warrant careful prospective study. Nevertheless, there have been major advances in the therapy of hepatitis B, and achievement of this goal is in sight.

4. Develop sensitive, specific, and non-invasive means of assessing disease stage (i.e. extent of fibrosis) in chronic liver disease. Multiple publications have assessed the use of routine laboratory tests to predict the presence of advanced fibrosis in patients with

hepatitis C, hepatitis B, and nonalcoholic steatohepatitis. No combination of tests is totally accurate and these approaches do not reliably detect early stages of fibrosis. Imaging tests for fibrosis are improving; one promising method is elastography, which measures the degree of stiffness of the liver. Prospective studies of elastography are now being developed, which should demonstrate the sensitivity and specificity of this technique. Meanwhile, more basic research on use of magnetic resonance and molecular imaging to detect fibrosis is being encouraged and actively pursued.

5. Develop sensitive and specific means of screening individuals at high risk for early hepatocellular carcinoma. Preliminary studies using gene expression arrays and proteomics have provided several possible targets for early detection of HCC, but none have been subjected to critical clinical evaluation. Meanwhile, standard assays for screening such as alpha-fetoprotein, alpha-fetoprotein L3, and des-gamma-carboxy prothrombin are now being evaluated critically for their sensitivity and specificity.

6. Develop means to prevent gallstones. While genetic markers for gallstone development have been identified in mice and are being applied to human populations, none have revealed targets for possible therapy or prevention of gallstone formation.

7. Elucidate the cause of biliary atresia. This goal is the specific focus of the Biliary Atresia Research Consortium (BARC), first funded in 2003, which now consists of 10 clinical centers and a data coordinating center. BARC has initiated both retrospective and prospective studies of children with biliary atresia, as well as a controlled trial of corticosteroid therapy during the post-operative period of hepatoportoenterostomy. The Consortium has also received funding for three ancillary studies directed at the etiology of biliary atresia, focusing on either genetics, proteomics, or gene expression arrays. A meeting with sessions on etiology of biliary atresia has been organized by the NIH for September 11-12, 2006.

8. Improve the safety and define optimal use of living donor liver transplantation. Living donor organs are currently used in approximately 9 percent of pediatric and 5 percent of adult liver transplants in the United States. In the last year, the results from the "Adult-to-Adult Living Donor Liver Transplantation Cohort Study" (A2ALL) showed the importance of transplant center experience in recipient outcome. Further studies from this study and in pediatric liver transplantation are likely to further define optimal use and safety of this life-saving procedure.

9. Develop standardized and objective diagnostic criteria of major liver diseases and their grading and staging. Preliminary meetings have been held on this topic by the NIH in collaboration with the American Association for the Study of Liver Diseases, and agreements in co-supporting this initiative have been developed. Early attempts have been made at standardizing diagnosis of primary sclerosing cholangitis and hepatitis B, but none have yet been published or accepted.

10. Decrease the mortality rate from liver disease. The ultimate goal of the Action Plan for Liver Disease Research is to decrease morbidity and mortality from liver and biliary disease in the United States. One difficulty in assessing this goal is the lack of consistently reliable data on the prevalence, incidence, and death rates from liver disease. A major source of information is the National Center for Health Statistics (CDC) and their yearly publication of Vital Statistics for the United States. Mortality rates in these reports are based upon death records, which can be unreliable, but are consistent enough to measure trends. Another problem is that publication of Vital Statistics are 2 to 3 years delayed, so that the most recent results are currently from 2003. For the purpose of this goal, overall numbers of deaths, death rates, and age-adjusted death rates are obtained from the Vital Statistics report on death rates for 113 Selected Causes. The overall rates of liver and biliary disease deaths are assessed using the totals of relevant ICD codes in this listing, including B15-B19 (Viral Hepatitis), C22 (Malignant Neoplasms of the Liver and Intrahepatic Bile Ducts), K70, K73-K74 (Chronic Liver Disease and Cirrhosis), and K80-82 (Cholelithiasis and Other Disorders of the Gallbladder). The age-adjusted death rates for 2000-2003 are shown in Table 3 below.

Table 3. Age-Adjusted Death Rates per 100,000 population

Diagnosis	**2000**	**2001**	**2002**	**2003**
Chronic Liver Disease and Cirrhosis	9.5	9.4	9.4	9.2
Viral Hepatitis	1.9	1.8	2.0	1.8
Malignant Neoplasms of the Liver and Intrahepatic Bile Ducts	4.7	4.7	5.0	4.9
Cholelithiasis and Disorders of the Gallbladder	1.0	1.0	1.0	1.0
Total: Liver and Biliary Disease	17.1	16.9	17.4	16.9
Total Number of Deaths	**47,635**	**48,068**	**50,076**	**50,052**

While the total numbers of deaths from liver and biliary disease increased slightly over the four years, the age-adjusted death rates were stable. Secular trends in death rates from liver and biliary diseases are likely to lag several years behind advances in research and development of improved means of diagnosis, monitoring, treatment, and prevention of liver disease.